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# Hepatocytes and Their Role in Metabolism

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## Abstract

Liver is one of the vital organ that performs many functions in the human body. Prominently it acts as a metabolizing organ for the body. This chapter elaborately describes hepatocytes along with their morphological features. In addition, it explains the structure of hepatocytes and different parts such as kupffer cells, hepatic stellate and hepatic sinusoids. Moreover present chapter elaborates the varieties of functions that hepatocytes perform such as filtration of blood, acting as a viral incubator, lipophagy and regulation of insulin and glucose. This chapter also explains hepatic injury that is caused by chronic consumption of alcohol along with the mechanism behind it.

**Keywords:** liver, hepatocytes, kupffer cells, viral incubator, lipophagy

## 1. Introduction

Liver is one the most vital organ of the human body and it is the largest among all other organs found in humans. There is incomplete separation of liver into lobes. These lobes are covered externally by a thin capsule of connective tissue. Liver is made up of different kinds of cells which interact with one another to perform specified functions. Hepatocytes or hepatic parenchymal cells are approximately 60% of the total cells found in the liver. Hepatocytes hold 80% of total volume of the organ. Hepatocytes are arranged into laminae in such a way that they connect with each other forming a 3 dimensional lattice. The space between the lattices is filled by hepatic sinusoid that performs the function of providing nourishment to the parenchymal cells of the 3 dimensional lattice. Other than the lattice, sinusoids and the non-parenchymal cells form the remaining volume of organ. The different types of non-parenchymal cells found are the inter-luminal kupffer cells, sinusoidal endothelial cell and perisinusoidal stellate cells [1].

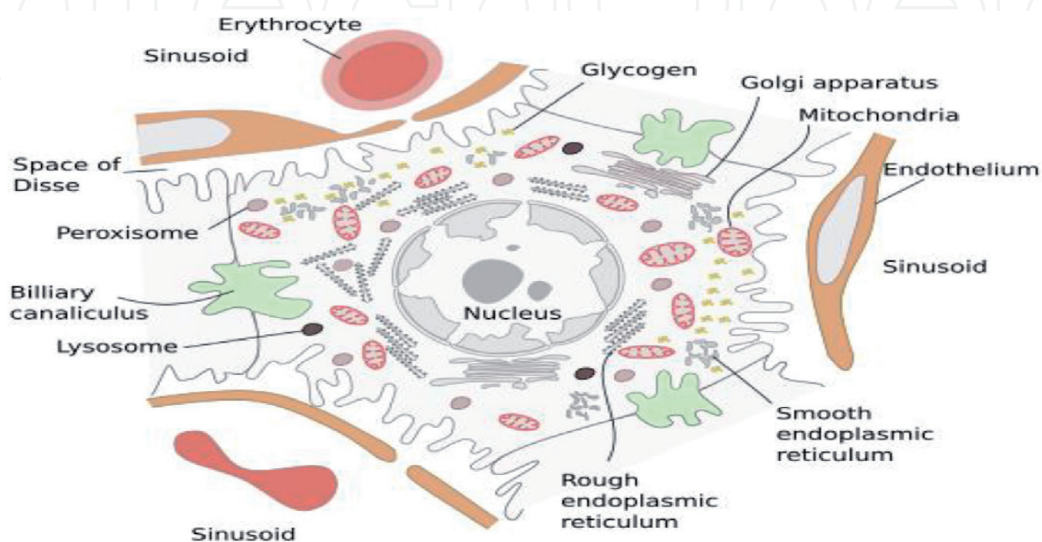
When blood passes through the liver the hepatocytes behave as a filter for blood that enters the liver. This behavior of liver helps in production of plasma protein and in endocytic uptake of variety of substances like lipid, trophic agents and growth factors. As liver performs the function of purification and is always in contact of agents like alcohol, excessive fat, pathogens or drugs, it is at higher risk of damage by these agents. This chapter will briefly describe organelles of hepatocytes and the functions they perform in the body. Further the chapter will focus on the function of hepatocytes in metabolism. Moreover it will also explain the mechanism of hepatocyte damage [2].

## 2. Morphology

The structure of hepatocytes is polyhedral in nature. It contains many faces but generally it is 6 in number. These faces are connected with face of other hepatocytes or in some cases it is in contact with sinusoids. Hepatocytes generally have diameters around 20 to 30  $\mu\text{m}$ . They have a round shaped nucleus in the center of cytoplasm. Approximately 25% of hepatocytes found in an adult human contain two nuclei instead of one. Most of these nuclei contains twice the number of chromosomes than a normal cell; thus are deemed tetraploid. In the nuclei, heterochromatin are scattered. The presence of mitotic hepatocytes is not seen generally in normal conditions. However their number increases in conditions like liver injury or in the process of regeneration. Depending upon the physiological state, the cytoplasm of the hepatic cell varies and is influenced by fat or glycogen depots. In a hepatocyte, as many as 100 mitochondria can be seen. Moreover the number of Golgi apparatus found in a hepatocytes accounts to approximately 50. Each Golgi apparatus are arranged in 3–5 cisterns. These cisterns are located near biliary canaliculi, small canal like structures that collecting the bile secreted by hepatocytes. Peroxisomes found in hepatocytes are in numbers of 200 or 300 which is more than found in normal cells (**Figure 1, Table 1**) [3].

### 2.1 Kupffer cells

Kupffer cells are the macrophages that reside in liver and are the highest number of resident macrophages in body. Kupffer cells are basically phagocytes that remove pathogens that in the circulation. Their presence in hepatic sinusoids allows them to perform the above said function efficiently. They also act against substances which are immunoreactive that enter through the portal circulation from the gastrointestinal tract. As Kupffer cells act against immunoreactive substances that enter from the GIT to portal circulation so they can be regarded as a barrier in the gut. It inhibits many inflammation that may occur due to these immunoreactive substances by destroying them in hepatic sinusoids. The Kupffer cell also plays a major role in clearing the dead red blood cells and comprise the mononuclear phagocytic system due to its phagocytic activity. Though Kupffer cells plays a major role in protecting the liver from injuries due to alcohol, drugs or toxins, however their



**Figure 1.**  
*Hepatocyte ultrastructure [3].*

Hepatic cell	Function of the cell
Parenchymal Hepatocytes	Chief cell of the liver, synthesis, storage, degradation of portal substance, metabolism, endocrine and exocrine function.
Non parenchymal cells	
Sinusoidal endothelial cells	Fenestrated plexus allows contact of portal blood with hepatocytes.
Kupffer cells	Liver phagocytes, release cytokines.
Stellate cell	Injury, precursor to myofibroblast, vitamin A storage.
Cholangiocyte	Transport bile, secrete bicarbonate and water.

**Table 1.**  
*Hepatic cell type and their functions [4].*

inflammatory response leads to conditions like chronic inflammation in liver which may be due alcoholic as well as non-alcoholic liver disease [5].

2.2 Hepatic sinusoids

The hepatic sinusoids are covered by specific endothelial cells that leads to formation of a barrier, which is porous in nature, that aid in exchange of materials among the hepatocytes and blood. The endothelial cells helps the clusters of differentiation markers such as CD14, CD16, CDw32, CD36, CD54, CD13 and CD4. They possess specific phenotype for portal venules, capillary endothelium, and terminal hepatic venule. It can be seen that the endothelium of portal tract arterioles, branches of portal vein and central veins binds with *U. europaeus* lectin and eventually stains CD34 and CD31 positively [6]. However sinusoidal endothelium in the majority of lobules are generally negative for CD34 and laminin. Positive staining of sinusoids is seen with carcinoma of hepatic cells as they stain sinusoid like vessels. [7, 8] Sinusoidal lumen contains cells such as kupffer cells, macrophages which can be seen by immunostain for CD68. Activated kupffer cells are positive with DPAS and muramidase [9, 10] .

2.3 Hepatic stellate cells

Hepatic stellate cells belong to the family of myofibroblasts. Stellate cells show their activity in the process of fibrogenesis and regulate flow of sinusoidal blood [11, 12]. They play the role of antigen presenting cells as well. Stellate cells during the childhood or adolescence phases are positive for actin whereas they are negative in adults and become positive only when there is any pathological condition [13]. Whereas in the case of synaptophysin, which is one of the main synaptic vesicle protein p38 and is encoded by the SYP gene, activated as well as resting stellate cells are positive. Stellate cells normally cannot be seen in a healthy liver whereas in pathological conditions they can be identified by vacuolated cytoplasm and a nucleus that becomes scalloped. Hepatic stellate cells are also related to the synthesis of collagen [14, 15].

3. Function of hepatocytes includes

Hepatic cytochromes P450 enzymes found in hepatocytes are one of the major enzymes that metabolize drugs. Hepatocytes also act a factory for protein and

biliary secretion. Moreover hepatocytes also behave as an endocytic blood-filtering machine. Hepatocytes aid in detoxification of blood.

### **3.1 Hepatic cytochromes P450 involved in drug metabolism**

The cytochromes P450 are terminal oxidase that comes under the superfamily of hemoproteins. This super family P450 has around 154 genes that can be seen in case of 23 eukaryotes in both plants and animal along with 6 prokaryotes. Among all the isoform of CYP450, CYP1, CYP2 and CYP3 are known to play important roles in majority of drug metabolism. P450 are responsible for catalyzing some of the reactions such as hydroxylation, dealkylation, and oxygenation. These cytochromes also have ability to catalyze reductive reactions where the metabolite produced from the reaction leads to inactivation of P450 [16].

Most xenobiotics are eliminated from body after undergoing chemical modification. The process of chemical modification of drug can be referred as biotransformation. In the process of biotransformation, lipophilic drugs are rendered more hydrophilic so that they can be excreted easily. Biotransformation occurs through two phases namely: Phase I and Phase II. Phase I reaction is also termed as functionalization reaction whereas Phase II reaction is called as conjugation reaction. In phase I reactions, the parent compounds undergoes oxidative processes to form more polar metabolites. In some case more reactive metabolites are also produced. The Phase I reactions are broadly of three types namely oxidation, reduction and hydrolysis. In phase II reactions, the parent compound or its Phase I metabolites are conjugated with endogenous substances like sulfate, glutathione or glucuronic acids to form a more water soluble and less toxic product that easily excrete out from the body.

Examples of Phase II reactions are

- i. Glucuronide conjugation: Compounds like Paracetamol, aspirin, chloramphenicol that are having carboxyl group or hydroxyl groups are conjugated with glucuronic acids.
- ii. Acetylation: occurs in compounds that has either amino or hydrazine in their structure. Examples of such compounds are sulfonamide, clonazepam.
- iii. Methylation: is generally seen in compounds like adrenaline, methyl dopa or histamine which contain amines or phenols in their structure.
- iv. Sulfate conjugation: A phenolic compound also may undergo sulfate conjugation as well.
- v. Glycine conjugation: Compounds such as salicylates which contain carboxylic group gets conjugated with glycine.

Metabolism of diverse ranges of xenobiotic are carried out by enzymes such as cytochrome (CYP) and flavin monooxygenases. CYP are found in liver predominantly and are also found in organs like gastrointestinal tract (GIT), lungs and placenta. 16 gene families and 29 sub families of CYP are found in human beings. Among these families, family 1, 2 and 3 are mostly responsible for biotransformation of xenobiotic. Most abundant CYP found in liver of adult humans is CYP3A4. CYP450 are also known to express more than 2000 mutation and ultimately shows polymorphisms. Some of the CYP also shows single nucleotide polymorphism (SNP). Some important polymorphism are seen in 1A2, 2C9, 2C19 and 2D6. The



genetic variation seen in the polymorphs are Mendelian inherited and are responsible for the catalytic variation they show in towards xenobiotic. Due to polymorphism, pharmacokinetic as well pharmacodynamics activities of drugs may show variations. When variability is seen in plasma concentration of drugs, it may lead to either toxicity due to exaggerated plasma concentration or suboptimal actions may be seen when plasma concentration is not achieved. If a new drug is metabolized by polymorphic enzyme then it can be considered as a drawback for the new drug because of the variation that can be shown to by the polymorphic enzyme [17, 18].

### **3.2 The hepatocyte as a protein and biliary secretion factory**

Hepatocytes contains many organelles that are secretory in nature as well as many mitochondria. Because of the presence of large number of endoplasmic reticulum and golgi bodies, the secretory activity of hepatocytes get overshadowed. Generally proteins that are secreted from hepatocytes initiates with ribosomal synthesis after which the polypeptide formed get transported into the lumen of endoplasmic reticulum then it reaches the golgi apparatus where secretory vesicles of golgi apparatus encloses the protein and transport it through exocytosis from hepatocytes [19, 20]. The major proteins that are secreted from hepatocytes are namely albumin, fibrinogen, transferrin and clotting factors. Serum proteins are the most prominent proteins secreted by hepatocytes [21–23]. It is important in context of bile production as well as in production of complex molecular soap that contains conjugated bilirubin, bile acids, electrolytes and phospholipids. Bile has a role in emulsification of fats and their digestion in the intestine as well as in removing xenobiotics and waste products that are produced endogenously. Synthesis of bile takes place in hepatocytes and is then transported to the bile canaliculi. Because of osmotic gradient bile moves through ductules and eventually reaches bile duct. During the transit, the bile is further modified by cholangiocytes and ductular epithelial cells [24]. Then bile goes into the gall bladder and it is released into intestine when needed. An amount of approximately 800 ml bile is secreted daily in the gut. The apical surface of hepatocytes because of thier structure, are tolerant to the bile environment. The apical domain also helps in synthesis, transportation and release of bile acids. Transportation is carried out by the ATP-dependent ABC transporter [25]. Transportation of cytotoxins and foreign substances is carried out by the multidrug resistance protein 1 as well as the multidrug and extrusion protein 1. The remaning content of bile like sulfate conjugates and conjugate bilirubin are exported through the bile salt export pump and multidrug resistance related protein 2. Aquaporin types such as aquaporin 0 and aquaporin 8 carry out the transportation of water to bile [26]. Most of the apical membrane protein moves through transcytosis whereas transporters such as the ABC transporter comes either from Golgi apparatus or through subapical endosomes [27, 28]. The sinusoidal surface is made up with basolateral membrane that makes the connection with the portal blood. Sinusoidal surfaces possess receptosr such as tyrosine kinase and trophic receptors. Moreover it also contains ABC transporter that performs the function of retrieving bile acids and other component sof bile from circulating blood. Conjugated bile acids which are water soluble is retrieved by the help of a transporter called sodium taurocholate cotransporter (NTCP) whereas water insoluble bile acids are retrieved with the help of organic anion transporting polypeptides [29, 30].

### **3.3 The ultimate endocytic blood-filtering machine**

Solute transporters perform the task of transporting bile acids whereas the protein that are found in the sinusoidal membrane plays an important role in

internalizing essential components from blood through hepatocytes. Liver being the first organ that is in contact with the nutrients that comes to the gastrointestinal tract, it has evolved into a kind of biological filter that filter out unwanted and potentially damaging substances that could reach those organs which do not have the ability to detoxify them. Liver cells, by the process of endocytosis, internalize materials that are present in extracellular matrix. There are many endocytic mechanisms found in the hepatocytes such as the fluid-phase endocytic mechanism as well as caveolae-based endocytosis. However the most prominent endocytic mechanism is receptor mediated endocytosis (RME) [31, 32]. Hepatocytes are remarkably capable of RME. In the process of RME, basolateral plasma membrane binds with extracellular ligands that present in blood plasma followed by incorporation via clathrin coated pits. When they enter the cell the receptor, ligand and the carrier protein are transported to a different destination within the cell, and are then recycled back and finally degraded by the action of lysosomes and endosomes. Trafficking of endocytic vesicles are controlled by Rab GTPases. Rab GTPase is an enzyme which assists in regulating various steps in membrane trafficking, such as vesicle formation, vesicle movement along actin and tubulin networks, and membrane fusion. Which basically selects specific protein for binding [33, 34]. Rab effector also performs other functions such as vesicle fusion and remodeling of membrane. Uponn ligand stimulation, internalization of half of the insulin along with EGF receptors through clathrin coated pits takes place within one minute [35]. Due to this great ability of endocytosis, hepatocytes are capable of performing the task of filtering blood which enters the hepatic portal system [36].

### **3.4 Regulation of systemic insulin and glucose**

After a meal, pancreatic  $\beta$ -cells secrete insulin in a pulsated manner. Insulin, by binding with insulin receptors, initiates the utilization of dietary glucose as well as its storage in the adipose tissue, muscles and in liver. Liver plays a major role in maintaining the homeostasis of glucose in the body. Hepatocyte stores around 100 g in glycogen polysaccharides [37, 38]. Postprandial release of insulin causes a decline in the blood glucose level. However to counteract this effect glucagon, a hormone that is secreted by pancreatic  $\alpha$  cells stimulate the utilization of glucose through the cyclic AMP- protein kinase A (cAMP-PKA) pathway [39, 40] Through RME hepatocytes clear around 80% of blood insulin before it reaches peripheral tissue [41]. The phosphatidylinositol 3-kinase- protein kinase B (PI3K-AKT) pathway initiates the storage of lipid and glucose. Whereas activation of the said pathway depends upon the endocytic uptake of insulin receptor [42]. When endocytosis of the insulin receptor takes place, it leads to dissociation of insulin ligand inside the endosomes and sorting of insulin receptors is done and through recycling pathway as they are trafficked back to the plasma membrane [43].

### **3.5 Endocytosis of two types of transferrin receptors (TfRs) is key for iron homeostasis**

One of the essential functions that is performed by liver is maintaining systemic iron homeostasis. Iron is a vital component in processes like cellular function, gene transcription, DNA replication and mitochondrial respiration [44, 45]. The human body depends on the dietary sources to fulfill its iron requirements as it is not produced in the body itself. This iron gets stored in the liver cells and macrophages [46]. There are two different endocytosis mechanisms through which iron storage and release takes place. Within the circulation, iron gets circulated by combining with a protein called as transferrin. Transferrin acts a ligand for the transferrin

receptors (TfRs). There are two types of transferrin receptors namely TfR1 and TfR2 which are found in different tissues and play a major role in homeostasis of iron [44, 45, 47]. TfR1 is abundantly expressed in the body and these receptors are concerned with iron uptake into the cells. Whereas TfR2 are found in erythroid cells and hepatocytes. These receptors aid in sensing of the presence or absence of iron in the human body and eventually helps in maintaining the homeostasis of iron [48]. Iron transferrin complex binds to the transferrin receptor and through a clathrin-mediated endocytosis process is internalized. Afterward the complex dissociates inside the cell and transferrins along with TfR receptor are transported back to the cell membrane [49]. The iron that remains in the endosome is transported to the cytoplasm with by a transporter called DMT1. In the cytoplasm iron complexes with another protein called ferritin. The majority of the ferritin stays in hepatocytes and sequesters around 4000 atoms of iron, making them available to structures of sub-cellular level such as DNA [50]. Moreover, hepatocytes also regulate iron release into the circulation by stimulating cells which are rich in iron stores such as macrophages and Kupffer cells [51]. TfR2 which is responsible to sense the level of iron in circulation stimulate the release a peptide called as hepcidin from liver cells whenever iron levels exceed normal. Hepcidin binds with ferroportin, an export transporter of iron [52, 53]. Hepcidin initiates ferroportin degradation in the endosomes by stimulating endocytosis and eventually reduces the export of iron and promotes its storage [54]. Hepatocytes are different from other epithelial cells as they participate in the internalization of iron through TfR1 and maintain homeostasis of with TfR2.

### **3.6 Lipoproteins, lipid droplets (LDs), lipolysis, and lipophagy**

The liver plays an important role in metabolism of lipid. Liver act as a depot for storage of lipid that are taken up from circulation. Breakdown and release of the stored lipid also takes place through liver. Dietary lipids are taken up by the liver cells as chylomicron remnants, although a significant amount of the lipid is released back into the blood in the form of very low-density lipoprotein (VLDL). Assembly of VLDL and translation and translocation of protein apoB100 inside the rough endoplasmic reticulum lumen occur simultaneously and binds to various neutral lipids. The lipoproteins which are secreted deliver lipid to tissues such as muscle or adipose either for storage or for utilization as an energy source. Hepatocytes clear 80–90% of these lipids from the blood stream [55]. Internalization of lipoproteins present in plasma into clathrin-coated vesicles is done by hepatocytes by the process of RME [56]. LDLR is the low-density lipoprotein receptor which helps lipoprotein-borne cholesterol enter into cells. LDLR identifies the surface proteins such as ApoE and ApoB100 present on low density lipoproteins and act as a station for retrieval of circulating lipids [57]. Conditions which affect the process of endocytosis of lipoprotein hugely impacts the level of cholesterol in the circulation and are the major reason for disease associated with heart and blood vessels [58]. Cholesterol, in the form HDL, also come back to the liver from macrophages that are present in artery as well as from peripheral tissues by a process called reverse cholesterol transport. Hepatocytes also takes up enterocyte-derived chylomicrons which contains retinyl esters (REs). Very small amounts of RE is taken up by hepatocytes for storage whereas maximum amounts are transported to hepatic stellate cells [59–61]. In endoplasmic reticulum lipid droplets (LDs) biosynthesis takes place leading to distention of neutral membrane lipids to cytoplasm [62]. Liver contains different types of lipolytic enzymes. These lipolytic enzymes, adipose triglyceride lipase (ATGL) and this family of enzymes act as catalyst in lipolysis of triglycerides and catabolism of LDs present in cytoplasm [63]. Moreover carboxylesterases perform the task of mobilizing triglycerol (TAG) from hepatic cells and mediate distribution



of stored fatty acids from LDs present in cytoplasm to VLDL which are formed in endoplasmic reticulum [64, 65]. This process of autophagy also is critical in LDs turnover. Lipophagy is a process where LDs are engulfed by hepatic autophagic membrane to form autophagosomes, then by the action of autolysosomes, LDs are broken down with by acidic lipase and hydrolases [66].

### **3.7 The hepatocyte as a viral incubator**

Liver being one the most vascular metabolizing organs, a large amount of blood enters is filtered. However, as liver receives such a huge amount of blood, it is always exposed to variety pathogens such as bacteria, virus or fungus. To counteract these pathogens hepatocytes release proteins, which in turn lead to stimulation of an innate immune response [67]. However some of the viruses by pass this defense mechanism of liver and enter the hepatocytes. Hepatitis B virus (HBV) and hepatitis C virus C (HCV) are viruses that enter hepatocytes. Infection caused by either these two can lead to severe liver disease [68]. HBV is a DNA virus and belongs to the family of Hepadnaviridae, it enters hepatic cells through a receptor called Na + taurocholate cotransporting polypeptide (NTCP) which is present on the surface of sinusoidal plasma membrane [69]. HBV is taken into hepatocytes by the process of endocytosis whereas there is no concrete idea about their escape [70]. According to studies, HBV replicates and releases infectious particles by hijacking the vesicular components such as multivesicular endosomes and autophagosomes [71]. Viral genomes enter the nucleus to undergo transcription, where the pre-genomic RNA gets to cytosol and undergoes the process of reverse transcription and packs the resultant DNA into icosahedral nucleocapsid [72]. HBV then utilizes the secretory ability of the liver cells to release mature viruses into the circulation.

HCV is an RNA virus which belongs to Flaviviridae family. It enters hepatocytes by posing itself as a lipoprotein particle. Mature virus expresses two kind of apolipoproteins namely E1 and E2 on their surface that eventually leads to binding to receptors such as LDLR and CD81, which are found in sinusoidal membrane of hepatocytes, leading to internalization of virus by the process of RME [73]. Then the virus fuses with endosomes. Finally the RNA genome which freely acts as a template for synthesizing structural and nonstructural proteins of HCV. The core capsid and nonstructural protein namely NS5A promotes the assembly of nascent HCV near the endoplasmic reticulum [74]. Once they are assembled the mature virus particles are secreted out of the hepatocytes [75].

## **4. Hepatocyte injury**

Alcohol is known to cause hepatic injury but it is the metabolite of alcohol that is produced during metabolism which is hepatotoxic. In the initial stage of alcoholic liver disease, steatosis occurs; whereas in case of acute or chronic exposure to alcohol leads to accumulation of triglycerides as well as enhances the expression of lipogenic enzyme. Moreover, the enzymes which are responsible for fatty acid oxidation are down regulated [76]. Advanced stages of alcoholic liver disease are associated with conditions like fibrosis and cirrhosis. In hepatic fibrosis extracellular matrix protein gets deposited and forms scars such as those that occur in cutaneous wounds [77, 78].

### **4.1 Mechanisms of hepatocyte injury by excess alcohol consumption**

Hepatocytes are the site of alcohol metabolism. Metabolites of alcohol that are produced during its metabolism are the major reason of hepatic injury. Chronic

consumption of alcohol is major risk factor for hepatic injury. In reversible alcoholic liver disease, hepatocyte shows a condition called as steatosis where accumulation of cytoplasmic LDs have accumulated. Whereas in acute or chronic stages of liver disease triglycerides accumulate because of enhanced expression of lipogenic enzymes as well as down regulation of those enzymes which are concerned in oxidation of fatty acid. Moreover LD metabolism, specifically its catabolism, is hampered due to impaired lipophagy [79]. Additionally lipolysis is impaired through cytoplasmic lipases [80]. Fibrosis and cirrhosis are the characteristics seen in later stages of alcoholic liver disease. In the process of alcohol metabolism, alcohol is converted to acetaldehyde in the presence of an enzyme called alcohol dehydrogenase present in the cytosol. Acetaldehyde is converted to acetate in mitochondria. The acetate produced is utilized in the citric acid cycle for the formation of acetyl-CoA. For alcohol metabolism, co factor NAD<sup>+</sup> is required in large amount, so it is depleted and in turn the reduction –oxidation (redox) state of ethanol exposed hepatocytes is altered. This leads to dysregulation of carbohydrate and lipid metabolism as well as inhibition of NAD<sup>+</sup> dependent enzymes that are responsible prevention of hepatic injury [81]. Cytochrome P450 2E1 (CYP2E1) also metabolizes alcohol, in addition to alcohol dehydrogenase, and produces acetaldehyde along with highly reactive oxygen and hydroxyethyl radicals. These metabolites are capable of forming bonds with protein, DNA and lipids [82]. CYP2E1 also produces oxidative stress which is one of the major causes of alcohol induced hepatic dysfunction. Eventually oxidative stress leads to endoplasmic reticulum stress resulting in apoptosis of the hepatic cell, steatosis and inflammation due to build up of unfolded protein [83]. Moreover alcohol induces an increase in mitochondrial permeability leading to alteration in homeostasis of cellular energy and eventually apoptosis in addition to generation of reactive oxygen species [84]. These acetaldehyde and oxygen radicals are the major mechanism of liver injury as they stimulate hepatic dysfunction and inflammatory response [85]. Consumption of alcohol induces production of enzyme CYP2E1 and it reinforces this cycle of hepatic damage again.

## 5. Conclusion and future perspectives

This chapter illustrates that hepatocytes have the unique ability to perform a variety of functions. It can be called a jack of all trades. Hepatocytes perform the task of detoxification of blood in one hand and also does the packaging and secretion of components such as lipid, protein and bile. In addition they take up nutrients from the blood stream. However, if there is any kind of compromise in the functioning of liver related to membrane trafficking it can lead to many diseases like cirrhosis, hepatitis, fibrosis and even carcinoma of the liver. The present chapter elaborated on the functioning of liver and the associated condition of liver when there is a variety of malfunctions. Liver being the major organ in metabolism as well as in detoxification of blood and nutrient uptake, through a series of detailed future research on its function and effect of various pathogenic conditions on its functioning can be accurately estimated. This chapter concludes that an accurate estimate will eventually be a boon to develop better treatment of the disease conditions associated with liver.

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doi: 10.1146/

annurev-cellbio-100616-060439

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